Chapter 2

ACUTE RADIATION SYNDROME IN HUMANS

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INTRODUCTION

The importance of human sensitivity to ionizing radiation was recognized even before the detonation of the first nuclear weapon. However, the exact relationship of dose to human mortality is still not precisely known because clear human data are lacking, and analyses of human mortality have been based primarily on data from radiation accidents, radiation therapy patients, and atomic-bomb victims. These studies have been faulted because of the small numbers of subjects, imprecise dosimetry, or patients' preexisting health problems and treatments. Therefore, many studies with laboratory animals have been undertaken in an effort to define the relationship between radiation exposures and effects. Several comprehensive analyses of human data and animal data have been conducted in an effort to derive a dose-response for humans.

Information on humans and animals has made it possible to describe the symptomatology associated with the acute radiation syndrome (ARS). In humans, ARS is defined as the symptoms manifested after exposure to ionizing radiation, and is often called radiation sickness. From a physiological standpoint, ARS is a combination of subsyndromes. They appear in stages and are directly related to the level of radiation received (Figure 2-1). These subsyndromes begin to occur within hours after exposure and may last for several weeks.

PATHOPHYSIOLOGICAL SUBSYNDROMES

Radiation damage results from the sensitivity of cells to radiation, and those that replicate most rapidly are the most sensitive to radiation exposure. In descending order of sensitivity, these cell types are spermatogonia; lymphocytes; erythroblasts; other hematopoietic cells; cells of the small intestine, stomach, colon, epithelium, skin, CNS, muscle, and bone; and the protein collagen. Mature cells that are more highly differentiated appear to be the least affected by radiation. This difference in cell sensitivity is the basis for the distinction among the three subsyndromes of ARS.

In order of their occurrence with increasing doses of radiation, ARS is divided into hematopoietic, gastrointestinal, and neurovascular subsyndromes.

Each subsyndrome can be further divided into four stages: *prodromal, latent, manifest illness,* and *recovery.* Prodromal symptoms begin a few hours to 4 days after exposure. The severity, time of onset, and duration of symptoms relate directly to the exposure dose received. The latent period is a brief reprieve from symptoms, when the patient may appear to have recovered. This reprieve may last up to 4 weeks, depending on the dose, and then is likely to be followed by 2-3 weeks of manifest illness. The manifest illness stage is the most difficult to manage from a therapeutic standpoint, for this is the maximum state of immunoincompetence that the patient will suffer. If the patient survives the manifest illness stage, recovery is almost assured. Therefore, treatment during the first 6

weeks to 2 months after exposure is crucial to ensure recovery from a rapidly received, high dose (less than 5 Gy) of ionizing radiation.

Hematopoietic Subsyndrome

The target cells of the hematopoietic tissue are the stem cells. Their anatomical location in the bone marrow distributes them throughout the body. Dorsal exposure would maximize damage to the hematopoietic system, because the greatest percentage of active bone marrow lies in the spine and dorsal regions of the ribs and pelvis. Vertical exposure would be the least damaging per equivalent dose, due to absorption and consequent nonuniform dose distribution, thus sparing the dorsal marrow. A dose-dependent suppression of bone marrow may lead to marrow atrophy and pancytopenia. Prompt radiation doses of about 1-8 Gy cause significant damage to the bone marrow. Doses of approximately 3 Gy may result in death to 50% of exposed persons.[1] The biological response of bone-marrow stem and progenitor cells to radiation exposure is exponential in nature. For example, halving the dose received does not increase the survival of stem cells from 1% to 50%, but to only 10%. Therefore, shielding remains the best protection of bone marrow.

Prodromal symptoms may include nausea, vomiting, anorexia, and diarrhea. If severe diarrhea occurs during the first 2 days, the radiation dose may have been lethal. The hematopoietic prodrome may last up to 3 days. This is followed by about 3 weeks of latency, during which the patient will suffer from significant fatigue and weakness. The clinical symptoms of manifest illness appear 21-30 days after exposure, and may last up to 2 weeks. Severe hemorrhage from platelet loss and infection associated with pancytopenia from bone-marrow suppression are the lethal factors in the hematopoietic subsyndrome. Platelet counts of fewer than 20,000/mm^3 (hemocytometer counting chamber), decreased erythrocyte counts, and severely suppressed white cell counts (fewer than 1,000) may be seen. Clinical hematological studies (complete blood count with platelets) may follow a course similar to that shown in Figure 2-2. There is a progressive decrease in peripheral cellular elements with increasing radiation dose. Specifically, a 50% decrease of absolute lymphocytes within the first 24 hours, followed by a second drop within 48 hours, is pathognomonic of potentially lethal injury from penetrating ionizing radiation.

The nuclear accident in Chernobyl provided information indicating that the total hematological profile must be used in predicting the radiation dose.[2] As shown in Figure 2-2, the systemic granulocyte count will increase at varying times after exposure, and may result from increased chemotaxis due to cell damage after irradiation. This transient increase may provide a false low interpretation of dose, and therefore should not be used as the sole indicator of dose received. However, a lowered granulocyte count may indicate the beginning of an immunocompromised state, which will likely be followed by the onset of fever and possibly severe infection.

Overall, the systemic effects that can occur from the hematopoietic subsyndrome include immunodysfunction, increased infectious complications, hemorrhage, anemia, and impaired wound healing. Impaired wound healing may be due in part to endothelial damage, which significantly depresses the revascularization of injured tissue.[3]

Gastrointestinal Subsyndrome

The gastrointestinal subsyndrome overlaps the hematopoietic subsyndrome, but its consequences are more immediate. At radiation doses above 12 Gy, this subsyndrome supersedes the hematopoietic subsyndrome in lethality. Its prodromal stage includes severe nausea, vomiting, watery diarrhea, and cramps occurring within hours after irradiation, followed by a much shorter asymptomatic latent period of 5-7 days. Then the manifest illness begins, with vomiting and severe diarrhea accompanied by fever. At higher doses, bloody diarrhea, shock, and death may ensue.

The intestinal mucosa suffers severe pathological damage following radiation exposure. The turnover time of 3-5 days for intestinal mucosal epithelial cells explains the shortened latent period. Since severely damaged crypt stem cells do not divide, the aging mucosal lining is shed and not replaced. This results in loss of absorption and provides a portal for intestinal flora to enter the systemic circulation. Figure 2-3 depicts vascular coalescence, which also significantly decreases intestinal absorption abilities. Severe mucosal hemorrhage has been seen in experimental animal models (Figures 2-4 and 2-5). The overall intestinal pathology includes disturbance of absorption and secretion, glycocalyx disruption, mucosal ulceration, alteration of enteric flora, depletion of gut lymphoid tissue, and motility disturbances.[4]

Systemic effects of this subsyndrome may include malnutrition resulting from malabsorption; vomiting and abdominal distension from paralyticileus; dehydration, acute renal failure, and cardiovascular collapse from shifts in fluids and electrolytes; anemia from gastrointestinal bleeding; and sepsis from damaged intestinal lining.

Neurovascular Subsyndrome

This subsyndrome is difficult to define. The lethal dose is over 30 Gy, but there is little information on these doses for human exposure, and the causes of death are confusing.[1,3,5] Cardiovascular shock accompanies such high doses, resulting in a massive loss of serum and electrolytes through leakage into extravascular tissues. The ensuing circulatory problems of edema, increased intracranial pressure, and cerebral anoxia can bring death within 2 days.

The stages of the neurovascular subsyndrome are extremely compressed. The prodromal period may include a burning sensation that occurs within minutes,

nausea and vomiting that occur within 1 hour, and confusion, prostration, and loss of balance. During the latent period, apparent improvement for a few hours is likely to be followed by severe manifest illness. Within 5-6 hours, the overt clinical picture proceeds with the return of severe watery diarrhea, respiratory distress, and gross CNS signs. After receiving doses in this range, two victims of separate uranium or plutonium recovery accidents survived fewer than 48 hours, even though they received optimal life support in excellent care facilities.

The pathology of this subsyndrome may be due to massive damage of the microcirculation. This has been postulated as a causative mechanism in the damage of some organs. Preliminary experimental evidence indicates that the cause of initial hypotension may be an early, overwhelming surge of histamine released from degranulated mast cells.[5,6] In fact, animal models did not suffer this hypotension when pretreated with histamine (H_1) blockers.[7,8]

The radiation threshold for this dual subsyndrome is not as well defined as it is for the others. Experimental evidence indicates that 50 Gy will elicit the neuro-vascular subsyndromes. Whether the dose is 50 or 100 Gy is inconsequential; either is a supralethal dose resulting in severe performance decrement. Figure 2-6 shows the occurrence of radiation effects in relation to dose and time. Table 2-1 charts the pathophysiological events.

DETERMINANTS OF RADIATION EFFECTS ON HUMANS

Energy deposition, known as *linear energy transfer* (LET), can be correlated to the severity of damage to the tissue. Gamma and X rays, which are primarily responsible for ARS, pass through tissue almost unimpeded by the skin or protective clothing. Thick shielding (such as lead, concrete, or dirt) is required to protect a person from these radiations. These rays are called *low LET* because they do not leave a great deal of their energy behind. Exposure to gamma emitters (such as cobalt-60) results in an accumulation of the dose within the first few centimeters of tissue, followed by a gradual decline of the dose level to 50% at the radiation's exit from the body. In contrast, *high-LET* neutron exposure results in significant absorption of energy within the first few centimeters, with diminution of dose at increasing tissue depth. In these cases, unilateral radiation results in more uniform exposure with gamma than with neutron radiation. Bilateral or multilateral exposure increases the uniformity of dose in all cases.

Alpha and most beta particles have low energy levels and cannot pass through skin (high-energy beta excepted) or clothing. Therefore, internalization (ingestion, inhalation, or absorption through a wound) and systemic contamination with alpha or beta radionuclides must occur for these radioactive particles to cause problems. Once internalized, they are a significant threat, because almost all of their energy is deposited in a short path through tissue or even in a single cell.

Lethality Curve

The slope of a lethality curve is weighted heavily by data at each extreme of its distribution. In the majority of experimental cases, the ratio of the data points is less than 2, independent of species (Figure 2-7). The more inbred and homogenous the population, the steeper the slope. This fact underscores the importance of reliable dosimetry, not only in the experimental situation but also in accurately determining the human exposure doses after a nuclear accident. In a recent examination, this correlation of a steep dose-effect relationship (slope) was evaluated using available data from canine studies.[9] Purebred and inbred populations did not appear to be either more sensitive or more resistant than mongrels. Given the genetic heterogeneity of humans, this ratio has been useful in extrapolating from animal data to the human dose-response curve, and in defining a lethal dose of radiation that will kill 50% of the healthy, untreated, exposed personnel (the LD_{50}) within 30 to 60 days after exposure. In spite of the heterogeneity surrounding LD_{50} values, it "seems possible to conclude that the doses giving between 90%-95% mortality in most animal experiments are about twice those giving 5%-10% mortality."[10] In a recent review of animal data, a uniform dose normalized to the LD_{50} (D/LD_{50}) revealed that no deaths occurred when D/LD_{50} was less than 0.54.[11] When D/LD_{50} was greater than 1.3, mortality was 100%. Total survival in a population can apparently be changed to total mortality by increasing the dose by a factor of 2.4. Relationships between dose and lethality, drawn from a large number of animal studies, emphasize two important points on extrapolation to the human radiation response: *(a)* reliable dosimetry is extremely valuable, and *(b)* either therapy or trauma can significantly shift the dose-response relationship. An error in dosimetry of 0.5-1.0 Gy can result in large shifts along the dose-response curve, and effective therapy can increase the LD_{50} by approximately 1.0 Gy. The degree of trauma depends on the duration and intensity of the radiation exposure, and it can shift along the mortality curve.

Modification of Dose-Response Curve

Radiation lethality may be a consequence of changes in the cellular kinetics of renewal systems critical for survival.[12,13] If this is correct, then modification of the dose-response relationship is achievable by replacement of the mature functional cells or their essential factors, or by actual substitutions in the damaged cell-renewal system.

Factors that compromise or damage the hematopoietic system or the immune system will also negatively affect the dose-response curve. Severe trauma, poor nutritional status, and stress are in this category. Other factors that significantly modify the dose-effect curve are radiation quality, exposure geometry (such as partial-body exposure or nonuniform exposure), and dose rate.

Influence of Radiation Quality and Exposure Geometry on LD$_{50}$

Distribution of radiation dose (energy deposition) throughout the target tissue varies significantly with the energy and quality of radiation and with the geometry of the exposure. Figure 2-8 illustrates the effects of tissue depth on absorbed radiation dose from unilateral cobalt-60 and 1 MeV (million electron-volts) of mixed neutron-gamma radiations. To reconstruct the effects of an accidental exposure involving neutrons, we must consider the tissue depth of a large-animal model (such as the canine) and that of humans, relative to the absorption characteristics of these two different radiation types (gamma and neutron, 1 MeV).

Equivalent doses of different types of radiation, or of the same type at different energy levels, do not produce equivalent biological effects. However, the *relative biological effectiveness* (RBE) of two types of radiation can be compared. A significant number of studies establishes the LD$_{50}$ for hematopoietic death in canines at approximately 2.60 Gy for 1,000 kVp (plate voltage in kiloelectron-volts) of cobalt-60 radiation, or 2,000 kVp of X radiation. For lower-energy X radiation (50-250 kVp), an average dose of 2.28 Gy would yield this LD$_{50}$.[14-21] These values suggest an RBE of approximately 0.87 for radiation higher than the standard 250 kVp of X ray energy. Canine exposure to mixed-fission neutron-gamma radiation yields an LD$_{50}$ value of 1.48 Gy (compared to a derived value of 2.60 Gy for cobalt-60).[15] This results in an RBE of approximately 1.7. Using a neutron spectrum of similar energy, an LD$_{50}$ of 2.03 Gy (compared to 2.80 Gy for 1 MVp of X radiation) was determined to have an RBE value of 1.38.[22] An RBE value of approximately 2.0 has been reported for rhesus monkeys exposed to fission neutrons of 1 MeV energy (the LD$_{50}$ value was 2.60 Gy) and for X radiation of 300 kVp energy (the LD$_{50}$ value was 5.25 Gy).[23] A significant RBE has been observed in the rhesus (LD$_{50}$) using gamma-neutron exposure, compared to the RBE for 250 kVp of X radiation.[24,25] Several studies used mice to establish RBE values for fission and high-energy neutrons pertaining to X radiation and cobalt-60 radiation.[25-28]

A radiation dose delivered to hematopoietic stem cells in bone marrow is the most damaging to the organism. Therefore, unilateral exposure with either gamma or neutron radiation will result in nonuniform dose distribution, whereas bilateral or rotational whole-body neutron exposure will have a greater RBE. Unilateral exposure usually occurs in accidents or warfare. Exposure to any type of unilateral radiation can result in lower doses to stem-cell populations that are distant from the source, with a consequent rise in the LD$_{50}$ value (Table 2-2).

Influence of Trauma on LD$_{50}$

The combination of radiation exposure and trauma produces a set of circumstances not encountered by most military and civilian physicians. In combined injury, two (or more) injuries that are sublethal or minimally lethal when

occurring alone will act synergistically, resulting in much greater mortality than the simple sum of both injuries would have produced. The mechanisms responsible for combined-injury sequelae are unknown, but they can significantly increase the consequences of radiation exposure across the entire dose-response curve. It must be emphasized that the survival of a patient following exposure in the hematopoietic dose range requires *(a)* a minimum critical number of surviving stem cells to regenerate a competent host defense system, *(b)* the functional competence of surviving cells composing the specific and nonspecific immune system, or *(c)* effective replacement or substitution therapy during the critical postexposure cytopenic phase. Trauma alone, depending on its intensity, may effectively depress host resistance to infection.[29-35] When imposed on a radiation-injured system, it can be lethal. In most instances, trauma symptoms will either mask or exacerbate the first reliable signs of radiation injury. This will cloud the situation if one is relying on biological dosimetry and prodromal symptoms for estimation of dose. In addition, the choice of treatment in these cases should include consideration of not only the patient's initial status but also the condition that will exist 7-21 days later when the radiation effects are seen.

Relatively few animal models of combined injury are available for determining effective therapy. The few reported studies demonstrate the synergistic effect of combined injuries. Sheep were exposed to 4 Gy of mixed neutron-gamma radiation and then 1 hour later subjected to an abrupt overpressure; this resulted in increased mortality from 25% for irradiated-only animals to 50% for the combined-injury animals.[36] A rat model showed a synergistic effect when a 250-kVp X-ray dose (LD_{50}) was followed in 7 days by a low-lethal (5%) level of air blast.[37] Mortality increased from approximately 46% for the irradiated-only animals to 76% for the combined-injury animals, and was related to radiation-induced thrombocytopenia, which compromised normal coagulation and maintenance of the capillary endothelium.

An open skin wound (combined injury) markedly increases the chances of infection. The immediate closure of wounds has been recommended.[38] Mortality in mice from exposure to 5.1 Gy of gamma radiation alone rose from 25% to 90% when combined with open dorsal skin wounds occurring 2 days after exposure. If wounds were immediately closed, mortality decreased to 18%. Closing of the skin wound obviously affected the mechanism of pathogenesis.

In combined injuries, burns produce the most significant synergistic increases in mortality. The dog, pig, rat, and guinea pig have been studied as animal models.[34,39-43] Table 2-3 summarizes this synergistic effect on the lethality of combined radiation and trauma. As little as 0.25 Gy, combined with a burn of 20% body surface area, increased mortality in dogs from 12% to 20%.[43]

In the early 1980s, investigators performed the most comprehensive analysis to date of the effect of combined injury (thermal and skin wound) on lethality and on the suppression of host resistance to subsequent bacterial challenge.[44,45] In

addition, they used cobalt-60 gamma versus mixed-fission neutron-gamma radiations in various ratios of LD_{50} on mice that had either thermal injuries or skin wounds. The addition of fission-energy neutrons to gamma radiation significantly lowered the LD_{50} in radiation-only experiments to give RBE values as high as 2.5. The addition of trauma to radiation exposures also significantly reduced the LD_{50}. The effect of combined injury on lethality was dominated by radiation. The RBE did not change with the addition of trauma.

Injuries to the abdomen may present significant problems to the irradiated subject. Blast overpressure, blunt trauma, and penetrating trauma are all significant causes of abdominal injury. The impact of laparotomy or splenectomy in mice that had received whole-body radiation has been evaluated.[38] Exposure to 5.1 Gy alone caused mortality of 27%, whereas laparotomy or splenectomy alone caused an approximate 5% mortality. Splenectomy at 2, 4, or 8 days after irradiation increased the mortality to 60%, 75%, and 85%, respectively. Laparotomy combined with radiation caused maximum mortality when surgery was performed on day 8. The role of the spleen in nonspecific resistance to bacterial infection has recently been demonstrated.[46]

The impact of combined injuries on the radiation dose-effect curve depends on the intensity and the time of injury relative to radiation exposure.[47,48] The biological consequences of these combined injuries will significantly affect the patient's abilities to survive and recover, and will markedly increase the casualty burden on medical personnel. Those patients in Hiroshima and Nagasaki who suffered conventional trauma along with radiation exposure developed significant complications 2-3 weeks later, corresponding to the time of hematopoietic depression. Until the 1986 reactor disaster in Chernobyl, the victims of Hiroshima and Nagasaki provided the only documentation on human radiation injuries and associated trauma. Hospitalized Chernobyl victims also experienced medical complications associated with bone-marrow damage and immunosuppression.

Effect of Clinical-Support Therapy on LD_{50} Dose-Effect Curve

Modification of survival throughout the LD_{50} dose range is achievable using a simple regimen of clinical support to replace or substitute the depleted functional cells after stem-cell destruction. In the cases of large-animal models (monkey, canine, and swine) and the human, therapy is directed at replacing the functions of the granulocytes and platelets. Experimental work performed more than 20 years ago showed the efficacy of supportive care centered on systemic antibiotics and transfusions of fresh platelets. Several canine studies indicated that antibiotics, singly or in combination, were successful in reducing mortality in the LD_{50} range.[18,49-51] Combination antibiotics, in conjunction with fresh whole-blood transfusions and parenteral fluids, have been effective in controlling dehydration and thereby reducing mortality. Reports that hemorrhage is easier to control than infection may be traced to the fact that several types of opportunistic pathogens are capable of overwhelming a compromised host.[18]

In an attempt to determine the lowest dose at which spontaneous regeneration would not occur, the dose range was extended in a later animal study from 4.0 to 5.5 Gy, well into 100% lethality (LD_{100}). The dose of 4.2 Gy resulted in an LD_{100}. Survival was significantly increased with good clinical support. This support consisted of *(a)* several antibiotics (penicillin G, dihydrostreptomycin, and tetracycline) administered at the onset of fever (8-13 days after exposure) and continued until fever subsided for 3-4 days and white cell count was greater than 1,000/mm^3; *(b)* the infusion of fresh platelet-rich plasma from 50 ml of blood, given when blood platelet levels were below 5,000/mm^3 (10-12 days after exposure); and *(c)* fluid therapy (isotonic saline or 5% dextrose) given during the period of anorexia. Soft food was usually given during this period to entice the animals to eat. The success with these regimens supports the hypothesis that infection and hemorrhage are the main contributors to lethal consequences of radiation exposure in the hematopoietic subsyndrome range. Controlling infection during the critical granulocytopenic and thrombocytopenic phase is the limiting factor in successful treatment.[49,51]

These studies have been extended over a dose range that is capable of determining the shift in LD_{50} that is due to treatment. Figure 2-9 shows the shift in the canine LD_{50} from 2.60 Gy to approximately 3.39 Gy measured as midline tissue dose. This results in a dose reduction factor of 1.3. The treatment regimen was essentially the same as above, with the addition of the newer antibiotics, gentamicin and claforan (cephotaxime-S0$_4$).[15] These collective data indicate that modest clinical care consisting of the infusion of fluids, antibiotics, and fresh platelets is capable of shifting the LD_{50} by a factor of 1.5. A more intensive regimen of support, including use of a sterile barrier and selective decontamination of intestinal bacteria, should allow an even greater shift in the LD_{50}. It must be emphasized that the practical application of these concepts requires that the damage to the stem-cell system be reversible; that is, the surviving fraction of hematopoietic stem cells must be capable of spontaneous regeneration.

Exposure Geometry: Heterogeneous Partial-Body and Nonuniform Exposure

Partial-body exposure can result in death through irradiation of specific target organs, such as the brain, lungs, and gastrointestinal structures. However, significant variations in the hematopoietic subsyndrome and related lethality can be seen when portions of the active marrow are either shielded physically from exposure or receive a smaller radiation dose due to nonuniform dose distribution through the body tissue. The earliest report of a shielding effect on the hematopoietic system was in 1963.[52] Exteriorized spleens of mice were shielded, which increased the LD_{50} from 550 to 975 R (roentgens). It was concluded that the shielded spleen contained competent and mobilizable hematopoietic stem cells that were capable of totally repopulating the depleted marrow space and significantly modifying the hematopoietic subsyndrome's dose-effect relationship. Many later experiments supported this finding by shielding either the hind limbs or tails of mice. A further

comparison in mice has been made of the therapeutic efficacy of this autorepopulation versus the efficacy of autologous and/or syngeneic bone-marrow transplantation.[26] In this study, one leg was shielded from lethal total-body exposure, allowing stem cells of the shielded leg to reseed the irradiated marrow space. Another set of mice received a similar exposure with the shielded leg later amputated. The marrow contents were harvested by a grinding technique and then auto-transplanted. (The grinding allowed greater efficiency in the stem-cell harvest.) Results indicated that autorepopulation of the marrow was more efficient than marrow transplant.

A series of experiments using canines further illustrated the protective effects of partial-body shielding.[53,54] Large-animal models can not only illustrate the relationships between tissue depth and dose, but can also approximate the nonuniform effects of exposure for more reliable extrapolation to the human radiation response. Shielding the lower body indicated an approximately sevenfold increase in LD_{50}.[54] One report emphasized that considerable hematopoietic tissue may be spared by nonuniform exposures to cobalt-60 gamma radiation.[55] Results indicated that the greater the dose gradient and the more nonuniform the exposure, the greater the survival of stem cells that are capable of repopulation.

These canine experiments illustrate the complexity of determining the dose received during an accidental exposure. Accidental whole-body irradiation will most likely not be strictly unilateral, due to backscatter and reflection of the radiation. It is also possible that some body regions may be shielded. These factors, as well as the anatomical position of the exposed subjects, can either increase or decrease the total dose received. Shielding and nonuniform dose distribution can therefore differ markedly in how much hematopoietic tissue they spare. The biological response of marrow stem and progenitor cells to radiation is exponential in nature.

Considerations on Establishing the Human LD_{50}

Similarly, it is difficult to calculate accurately the dose that a human has received after accidental radiation exposure. Radiation quality or type, dose rate, shielding, exposure geometry, and coincident trauma can significantly modify the relationship of dose and response.

Several comprehensive analyses of human and animal data have been conducted over the years in an effort to derive a dose-response curve for humans. Some reports serve as landmarks, but none has been completely successful. The quest for an LD_{50} for humans began in the late 1940s and continues today.[10,56,57] The most recent activity on this subject has shifted from the United States to the United Kingdom, where interest from the British Home Office produced comprehensive analyses.[10,58,59] The suggestion emerging from these analyses—that the LD_{50} might be as high as 6 Gy (body surface, free-in-air dose)—was controversial in

light of the long-held view that the value was 4.5 Gy or less. The 6-Gy free-in-air dose corresponds to an approximately 4.5-Gy bone-marrow dose, and the 4.5-Gy free-in-air dose corresponds to a 3.6-Gy bone-marrow dose. The 1986 LD_{50} value of 1.54 Gy to the bone marrow added to the controversy and sparked new interest in resolving these discrepancies.[59]

Available data on uncomplicated radiation exposures to the human within the hematopoietic-subsyndrome range are relatively limited. The evidence to date (excluding the 1986 nuclear disaster in Chernobyl and the 1987 radiation isotope incident in Goiânia, Brazil) is from three sources: *(a)* twenty cases of radiotherapy with whole-body, bilateral exposure to gamma radiation; *(b)* two nuclear criticality accidents involving mixed neutrongamma exposure of nine persons, one of whom died; and *(c)* the cases of thousands of persons exposed to the nuclear detonations over Hiroshima and Nagasaki in 1945. The following descriptions of the radiotherapy patients and nuclear criticality patients illustrate the type of information that, until recently, was used in determining the human LD_{50}.

Radiotherapy. Twenty adolescent patients (nineteen with Ewing's sarcoma and one misdiagnosed who actually had leukemia) were uniformly exposed to 3.0 Gy of whole-body cobalt-60 gamma radiation as a midline tissue dose at a dose rate of 0.2 Gy/minute.[60] All patients survived for at least 1 year. It appears that this experience would set the lower limit for the lethal dose at a dose greater than 3.0 Gy. However, several modifying factors must be considered. These patients were given excellent supportive clinical care during their hospital stay. They received fluids, electrolytes, and blood replacement (platelets for some) as necessary, and simple antibiotic treatment while under barrier nursing. It has been recently revealed that many of these patients received local radiation to the sites of the tumors before, and in some cases after, the whole-body exposure. These prior exposures complicate the picture because of possible abscopal effects on distant hematopoietic tissue. It is difficult to determine the effect of hospital-based care and support, but the Chernobyl experience and animal data point to a significant decrease in lethal consequences.

Radiation Accidents. Of many radiation accidents reviewed (Chernobyl excluded), two involved shielding, dose uniformity, and acute exposure (estimated as 2-10 Gy) that were comparable to LD_{50} values in humans. Both accidents were criticality accidents that involved fission neutrons, low-energy photons, and high-energy gamma rays. Four of the seven male workers exposed in the 1958 Y-12 Oak Ridge, Tennessee, accident and five of the workers exposed in the 1958 Vinca, Yugoslavia, accident are considered to have received relevant radiation doses.

Reconstruction of the Y-12 accident dose indicates a total marrow dose range of 3.25-4.40 Gy for upper limits to 1.9-2.6 Gy for lower limits, assuming lateral or anterior-posterior exposure.[10] These workers most likely were exposed to two

pulses separated by several seconds. The accident occurred during maintenance operations at a fuel-reprocessing plant. A uranyl nitrate solution was inadvertently allowed to collect, and a fission chain reaction began, followed by a second reaction and perhaps more. The first reaction probably gave the greatest part of the total dose to the workers. Seven persons received 1.0 Gy or more, and of them, four are considered to have received the higher homogeneous doses, which are more relevant.

Nausea and vomiting occurred in three workers within 2 hours after exposure, and one vomited on the second day. Diarrhea was not evident. Some complaints of soreness, fatigue, and weakness were registered. All showed hematological changes reflecting severe marrow damage. Hospital treatment was conservative, and the patients were discharged 39 days after exposure.

At Vinca, the exposure of five persons ranged from a lower limit of 1.8-2.3 Gy to an upper limit of 2.3-3.1 Gy,[10] occurring over several minutes when an unshielded research reactor temporarily ran out of control.[61,62] This led to the emission of a "softer" neutron spectrum than that which occurred in the accident at Y-12. Low-energy neutrons are not very penetrating, but do give rise to a measurable tissue gamma dose. Therefore, a calculation of marrow dose had to be estimated. Although the dose levels at both accidents were similar, the clinical responses of the victims differed significantly.

For the Vinca victims, severe nausea and vomiting occurred within the first hour. A larger dose to the superficial tissues was indicated by erythema, conjunctivitis, and loss of body hair. The most highly irradiated victim suffered severe diarrhea. Victims were nursed under sterile conditions, receiving fluids, electrolytes, blood-cell transfusions, and antibiotics. The hematological picture worsened through the 3 weeks after exposure, and five patients were injected with donor-matched bone-marrow cells at 4-5 weeks after exposure. The value of the marrow transplant is moot. It has been argued that the recipients were on their way to recovery and that the benefits of these transplants were temporary at best. One man, who received the highest dose of radiation, did not respond to treatment; he died of gastrointestinal complications on day 32.

PRESENT VIEW OF RADIATION EFFECTS ON HUMANS

Several new studies relate to the establishment of an LD_{50} for a low-LET radiation dose to the bone marrow of healthy young adults. These studies include several important observations that must be considered when estimating the radiation mortality response of humans. First, in selecting data groups for analysis, the influence of postirradiation clinical treatment must be taken into account. Carefully controlled experiments clearly indicate that treatment will elevate the estimate of the LD_{50} by as much as 30%.[63] The calculated LD_{50} of approximately 6 Gy for the Chernobyl patients treated for ARS also indicates a

benefit from intensive clinical support. This observation is reinforced by the fact that many of these patients had complicating burns, which have been shown to lower the LD_{50} in the Nagasaki victims and in studies of laboratory animals. These observations suggest that the British value of 4.5 Gy overestimates the bone-marrow LD_{50}, since this value is derived entirely from persons who received supportive therapy.[60] The data from the Ewing's sarcoma patients in this study seem particularly compromised, because these patients received not only antibiotics and platelets but also barrier nursing and possibly tumor pretreatment with X rays before receiving the 3 Gy of total-body radiation.[60] If this pretreatment with X rays can be confirmed, we must assume that the sensitivity of the patients to sub-sequent radiation therapy was reduced. These several factors suggest that anchoring the low end of a dose-response curve with these data is not justified.

The second observation to emerge from these new studies is the dependence of LD_{50} on dose rate, particularly at rates of 0.6 Gy/ hour or less, as seen in data from human experience and studies with laboratory animals.[11,64] This dependence is particularly important when attempting to use low-dose-rate studies as estimates of prompt LD_{50}. Table 2-4 shows a model for the relationship between dose rate and LD_{50}.[11]

The third observation is that the LD_{50} for the human cannot be modeled on a 70-kg animal. This is true even if the analysis is based on all animal studies to date, if the model is carefully controlled for body weight, and if the dose rate is below 0.5 Gy/minute. The LD_{50} may be more species-independent at prompt dose rates, where data from several large mammals, including humans, appear to con-verge.[65]

A fourth observation is that although the LD_{50} for the human may not be exactly like that of another 70-kg mammal, the slope derived from the animal model is much more credible than the unacceptably shallow slope observed in the Hiro-shima and Nagasaki analyses. These differences in slope may be due to differences in *(a)* the accuracy of dose determination, *(b)* the homogeneity of the sample populations for humans and animals, or *(c)* the postirradiation treatment. With no acceptable slope that can be empirically derived directly from human data, the recommendation is to use the slope obtained from the Oak Ridge National Laboratory animal model (Figure 2-10). The LD_{90} and LD_{10} should be taken as the values for the limits of the dose-response curve because the extra-polations are totally unreliable beyond that range. The slope should be expressed as the ratio of the LD_{90} to the LD_{10}. This expression maintains linearity over the entire curve and has a value of 1.9, which is in good agreement with other such values.[64,65]

The final observation is the degree of agreement that is emerging among the values for the LD_{50}, especially from the Hiroshima and Nagasaki data. Recently, a value of 1.54 Gy for the midlethal bone-marrow dose for Hiroshima was pub-

lished.[59] This value was derived from survey data relating the mortality of persons in wooden houses to their distance from the hypocenter of the bomb. Using preliminary calculations of dose versus ground range, the Hiroshima LD_{50} was determined to be 1.54 Gy.[59] However, if one uses the latest calculations, the value becomes 2.3 Gy to the bone marrow. This value is in general agreement with the reported value of 2.24-2.50 Gy, based on doses and essentially the same model.[66] Both of these values were skewed by the inclusion of data from deaths due to burns and blast effects. If one increases these values by 17.5% (the difference in LD_{50} for radiation only, and radiation combined with blast injuries and burns), the values increase to 2.75-3.0 Gy. Another recent analysis of the data from Hiroshima estimates the LD_{50} to be 2.72 Gy by correlating white blood-cell counts to the percentage of mortality. Considering the diversity of these analyses and the approaches by which they were derived, their agreement is remarkable. Even more remarkable is the fact that these values agree with the human values obtained 20 years ago for patients, when adjusted for bone-marrow dose and prompt dose rates.

There is good agreement among the data (particularly the recent data from Hiroshima and Nagasaki) that the NATO human LD_{50} should not be raised for healthy untreated persons. Based on the range of values discussed, the recommended value for the LD_{50} is 3.0 Gy to bone marrow (4.3 Gy free in air).

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